REMARKS

Status of the Claims

Claims 1-5, 9, and 18 have been amended. No new matter has been added. **Claims 1-5,9-14, and 18** are pending. Applicant respectfully requests reconsideration of the application in light of the amendments and the following remarks.

A. Response to Remarks

1a. The proviso in claim 1 is considered "new matter" because the negative limitation as amended does not have support in the disclosure (Office Action, page 3).

Claim 1 has been amended to recite that R3 is:

(ix) unsubstituted or substituted (C_1-C_6)-alkyl,

(x) (C_1-C_4)-alkyl substituted by one or more fluorine atoms, preferably a trifluoromethyl group,

(xi) unsubstituted or substituted (C_1-C_4)-alkyl-(C_6-C_{14})-aryl, unsubstituted or substituted (C_1-C_4)-alkyl-heteroaryl

(xii) (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylaminocarbonyl (C_1-C_4)-alkylaminothiocarbonyl, (C_1-C_6)-alkyl-carbonyl or (C_1-C_6)-alkoxycarbonyl-(C_1-C_6)-alkyl,

it being possible for the substitution of the alkyl radical by F, Cl, Br, I, CN, NH_2, NH-(C_1-C_{20})-alkyl, NH-(C_3-C_{12})-cycloalkyl, OH, O-(C_1-C_{20})-alkyl to take place singly or, on identical or different atoms, multiply by identical or different substituents, and it being possible for the substitution of an aryl radical by F, Cl, Br, I, CN, NH_2, NH-(C_1-C_{20})-alkyl, OH, O-(C_1-C_{20})-alkyl and/or (C_3-C_8)-heterocyclyl having 1 to 5 heteroatoms, preferably nitrogen, oxygen, sulfur to take

place singly or, on identical or different atoms, multiply by identical or different substituents.

The definition of R3 eliminate the need for use of negative limitations in Claim 1 and the compounds of Claim 1 are novel and patentable. Support for the above quoted recitation is found in the specification, for example, on page 7, lines 6-23, continuing on page 8, lines 1-5. Therefore, Applicants respectfully request withdrawal of the rejection of **Claim 1**.

2a. The response is silent about the support of new claim 18, the diseases as listed were not in the disclosure (Office Action, page 3).

Claim 18 has been amended to recite a method for the treatment of a tumor disease selected from the group consisting of prostate carcinoma, lung carcinoma, leukemia, paclitaxel- and vindesine-resistant tumors, and doxorubicin-resistant tumors, tumors of the stomach, tumors of the neck, tumors of the uterus, tumors of the head and neck, tumors of the large and small intestine, skin cancer, breast cancer, ovarian cancer, cervical cancer, pancreatic cancer, prostate cancer, hepatic cancer, renal cancer, skin cancer, cancers of the brain, cervical carcinoma, ovarian adenocarcinoma, glioblastoma, lung carcinoma, breast cancer, colon cancer and blood cancer, comprising administering a disorazole compound of the general formula Ia. Support for the diseases listed can be found in the specification, for example, on page 1, lines 19-21; page 2, lines 17-19; page 11 (Example 1), lines 2-6; page 16 (Example 8) , line 15. page 2, lines 17-19; and page 15, line 19. Applicants respectfully submit that the present specification

provides enabling support for **Claim 18** and withdrawal of the rejection thereof is respectfully requested.

3a. Applicant argues that the reference does not anticipate claim 3, which is composition claim. Examiner respectfully disagrees because the compositions claims are included in the rejection, when the compound is anticipated its composition is also anticipated. Composition is not separated from compounds (Office Action, page 3).

Claim 3 has been amended to recite a pharmaceutical composition comprising a disorazole compound of the general formula I as claimed in amended **Claim 1**. Support for the compounds of the general formula I is cited above. Applicants respectfully submit that the compound of the general I are novel and patentable and so are compositions containing them. Therefore, Applications respectfully request withdrawal of the rejection of **Claim 3**.

B. The Rejection Under 35 USC § 112, First Paragraph (Written Description)

1b. **Claims 1-5, 9-14** and **18** are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement because they contain a negative limitation that does not have basis in the original disclosure.

Claim 1 has been amended to recite that R3 is:

(xiii) unsubstituted or substituted (C_1-C_6)-alkyl,

(xiv) (C_1-C_4)-alkyl substituted by one or more fluorine atoms, preferably a trifluoromethyl group,

(xv) unsubstituted or substituted (C_1-C_4)-alkyl-(C_6-C_{14})-aryl, unsubstituted or substituted (C_1-C_4)-alkyl-heteroaryl

(xvi) (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylaminocarbonyl (C_1-C_4)-alkylaminothiocarbonyl, (C_1-C_6)-alkyl-carbonyl or (C_1-C_6)-alkoxycarbonyl-(C_1-C_6)-alkyl,

it being possible for the substitution of the alkyl radical by F, Cl, Br, I, CN, NH_2, NH-(C_1-C_{20})-alkyl, NH-(C_3-C_{12})-cycloalkyl, OH, O-(C_1-C_{20})-alkyl to take place singly or, on identical or different atoms, multiply by identical or different substituents, and it being possible for the substitution of an aryl radical by F, Cl, Br, I, CN, NH_2, NH-(C_1-C_{20})-alkyl, OH, O-(C_1-C_{20})-alkyl and/or (C_3-C_8)-heterocyclyl having 1 to 5 heteroatoms, preferably nitrogen, oxygen, sulfur to take place singly or, on identical or different atoms, multiply by identical or different substituents.

The current definition of R3 eliminates the need for the use of negative limitations in **Claim 1** and the compounds of **Claim 1** are novel and patentable. Support for the above quoted recitation is found in the specification, for example, on page 7, lines 6-23, and on page 8, lines 1-5. Applicants respectfully request withdrawal of the rejection of **Claim 1**.

Claim 2 has been amended to recite the compound of **Claim 1**, wherein R1 is hydrogen or part of a double bond to C5', and R2 is hydrogen, R3 is methyl and X and Y are, independently of one another, oxygen, sulfur, two vicinal hydroxyl groups, two vicinal methoxy groups, or part of a double bond. Support for "R3 is methyl" can be found in the originally filed **Claim 9** (Specification & Claims, page 30, line 8). **Claim 2**,

by virtue of its dependency on **Claim 1** is also free of negative limitations and therefore Applicants respectfully requests withdrawal of the rejection thereof.

Claim 3 has been amended to recite a pharmaceutical composition comprising a disorazole compound of the general formula I as claimed in **Claim 1**, a pharmaceutically acceptable carrier, diluent or excipient. The compound of amended **Claim 1**, as stated above, is novel and therefore the pharmaceutical composition of **Claim 3**, which comprises the novel compound is novel as well. Therefore, Applicants request withdrawal of the rejection of **Claim 3**.

Claim 4 has been amended to recite a method for the treatment of oncoses selected from the group consisting of tumors of the lung, the breast, the stomach, the neck , the uterus, the prostate, the head and neck, the large and small intestine, and the liver and the blood system; ovarian carcinoma, prostate carcinoma; glioblastoma; lung carcinoma; breast cancer; skin cancer; colonic cancer; renal cell cancer; hepatic cancer; pancreatic cancer; cervical cancer; and cancers of the brain, comprising administering a compound of the general formula Ia (as described in **Claim 4**), alone or in combination with a cytotoxic substance and/or an inhibitor of signal transduction, to an individual in need thereof. Support for the negative limitation in the description of the compound of general formula Ia can be found in the specification, for example, on page 8, lines 13-14. Applicants respectfully request withdrawal of the rejection of **Claim 4**.

Claim 5 has been amended to recite a method for the treatment of a disease in humans or animals which is based on the rapid and uncontrolled proliferation of

endogenous cells comprising administering a compound of the general formula Ia, with the proviso that the compound in which R1 is methoxy, R2, R3 are hydrogen, X is oxygen and Y is the part of a double bond is excluded, its tautomers, E/Z isomers, stereoisomers, including the diastereomers and enantiomers, and the physiologically tolerable salts thereof, to a human or animal in need of such treatment. Support for the negative limitation can be found in the specification, for example, on page 8, lines 13-14. Applicants therefore request withdrawal of the rejection of **Claim 5**.

Claim 9 has been amended to recite a method for the treatment of: benign or malignant oncoses in humans or animals selected from the group consisting of breast cancer, lung cancer, ovarian cancer, skin cancer, prostate cancer, colonic cancer, renal cell cancer, hepatic cancer, pancreatic cancer and cancers of the brain); inflammatory diseases selected from the consisting of bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, eczema, and allergic angiitis; inflammations mediated by eosinophils such as eosinophilic pneumonia; pulmonary infiltration with eosinophilia syndrome (PIE syndrome); urticaria; ulcerative colitis; Crohn's disease; psoriasis; or keratosis, comprising administering a compound of the general formula Ia (as described in **Claim 9**) to a human or animal in need of such treatment. Support for the negative limitation can be found in the specification, for example, on page 8, lines 13-14. And support for the listed diseases can be found in the specification, for example: on page 11 (Example 1), lines 3-6; page 11 (Example 2), lines 17-22; and page 12, lines 1-2; page 15, line 19. Applicant respectfully request withdrawal of the rejection of **Claim 9**.

Claims 10, 11, and 12 all depend from **Claim 9** whereas **Claim 13** depends from **Claim 12** and **Claim 14** depends from **Claim 3**. Support for amended **Claims 3** and **9** have already been described in detail above. Therefore, Applicants respectfully request withdrawal of rejections of **Claims 10-14**.

C. The Rejection Under 35 USC § 112 ,First Paragraph (Scope of Enablement)

1c. **Claims 1-5, 9-14** and **18** are rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for certain method of treatments does not reasonably provide enablement for all the method of use such as treatment of oncoses (**Claim 4**) , uncontrolled proliferation of endogenous cells (**Claim 5**), infective diseases, immunomodulatory action as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims (Office Action, page).

Claims 1 and **2** are compound claims and their rejection as method of treatment claims is inappropriate. Withdrawal of the rejection is respectfully requested.

Claim 3 has been amended to recite a pharmaceutical composition comprising a disorazole compound of the general formula I as claimed in **Claim 1**, a pharmaceutically acceptable carrier, diluent or excipient. The compound of amended **Claim 1** is novel and therefore the pharmaceutical composition of **Claim 3**, which comprises the novel compound is novel as well. Moreover, since **Claim 3** is a composition claim its rejection as a method of treatment claim is also inappropriate and therefore withdrawal of the rejection is respectfully requested.

Claim 4 has been amended to recite a method for the treatment of oncoses selected from the group consisting of tumors of the lung, the breast, the stomach, the neck

, the uterus, the prostate, the head and neck, the large and small intestine, and the liver and the blood system; ovarian carcinoma, prostate carcinoma; glioblastoma; lung carcinoma; breast cancer; skin cancer; colonic cancer; renal cell cancer; hepatic cancer; pancreatic cancer; and cancers of the brain, comprising administering a compound of the general formula Ia, its tautomers, E/Z isomers, stereoisomers, including the diastereomers and enantiomers, and the physiologically tolerable salts thereof, to an individual in need of such treatment alone or in combination with a cytotoxic substance and/or an inhibitor of signal transduction. Support for the listed diseases has been provided above. Therefore, Applicants respectfully request withdrawal of the rejection of **Claim 4**.

Claim 5 has been amended to recite a method of inhibiting mitosis in rapidly and uncontrolledly proliferating endogenous cells in humans or animals, comprising administering a compound of the general formula Ia as defined in **Claim 4**, to the humans or animals in need thereof. Support for the quoted recitation can be found in the specification, for example on page 19, lines 3-11; page 20, lines 7-9; and page 4, lines 14-17; and page 4, lines 18-20. Applicants submit the amended Claim 5 is fully supported by the specification and therefore withdrawal of the rejection thereof is respectfully requested.

2c. New claim 18 is drawn to various tumor diseases and a long list of tumor diseases are claimed. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating rapid and uncontrolled proliferation of endogenous cells comprising adimistering the compound of Formula Ia as in claim 5. (Office Action, page)

Claim 18 has been amended to recite a method for the treatment of a tumor disease selected from the group consisting of ovarian carcinoma, prostate carcinoma, glioblastoma, lung carcinoma, breast cancer , leukemia, paclitaxel- and vindesine-resistant tumors, and doxorubicin-resistant tumors, tumors of the stomach, tumors of the neck, tumors of the uterus, tumors of the prostate, tumors of the head and neck, tumors of the large and small intestine, tumors of the liver and the blood system, skin cancer, colonic cancer, renal cell cancer, hepatic cancer, pancreatic cancer, cancers of the brain and cervical carcinoma, comprising administering a disorazole compound of the general formula Ia, alone or in combination with a cytotoxic substance and/or an inhibitor of signal transduction, to an individual in need thereof. Support for the diseases listed can be found in the specification, for example, on page 1, lines 19-21; page 2, lines 17-19; page 11 (Example 1), lines 2-6; page 16 (Example 8) , line 15. page 2, lines 17-19; and page 15, line 19. Applicants respectfully request withdrawal of the rejection of **Claim 18**.

D. The Rejection Under 35 USC § 102(b) (1st Rejection)

1d. Claims 1-4 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by JANSEN et al. (Liebig Ann. Chem. (1994), 759-773). (Office Action, page 14)

The JANSEN reference does not anticipate **Claims 1-4** and **14** as it neither teaches structural variable R3 of the compound of general formula I, as recited in **Claim 1-3** and **14** nor the method for the treatment of oncoses of **Claim 4**. Therefore, Applicants respectfully request withdrawal of the rejections of **Claims 1-4** and **14**.

E. The Rejection Under 35 USC § 102(b) (2nd Rejection)

1e. Claims 1-4 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by IRSCHIK et al., (The J. of Antibiotics). (Office Action, page 14)

The IRSCHIK reference does not anticipate **Claims 1-4** and **14** as it neither teaches structural variable R3 of the compound of general formula I, as recited in **Claim 1-3** and **14** nor the method for the treatment of oncoses of **Claim 4**. Therefore, Applicants respectfully request withdrawal of the rejections of **Claims 1-4** and **14**.

CONCLUSION

In view of the above amendments and remarks, Applicants believe that all rejections of the pending claims are overcomed, and Applicants respectfully request the rejections thereof be withdrawn and the claims pass to allowance. Should the Examiner feel that a personal discussion might be helpful in advancing this case to allowance, the Examiner is invited to telephone the undersigned.

The Commissioner is authorized to charge any required fees, including any extension and/or excess claim fees, any additional fees, or credit any overpayment, to Goodwin Procter LLP Deposit Account No. 06-0923.

Respectfully submitted for Applicant,

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